TransCon™ PTH

Top-Line Data from Phase 3 PaTHway Trial

March 13, 2022

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TransCon PTH PaTHway Trial Top-Line Data at Week 26

- PaTHway Trial met primary and all key secondary endpoints
  - 78.7% of patients (48 of 61) treated with TransCon PTH achieved the primary endpoint, compared to 4.8% (1 of 21) of patients in the control group (p-value <0.0001)
  - Statistically significant improvements observed on all key prespecified secondary endpoints compared to control:
    - HPES Symptom measures: Physical domain score (p-value = 0.0038) and Cognitive domain score (p-value = 0.0055)
    - HPES Impact measures: Physical Functioning domain score (p-value = 0.0046) and Daily Life domain score (p-value = 0.0061)
    - SF-36v2® - Physical Functioning subscale score (p-value = 0.0347)
- TransCon PTH was generally well tolerated, with no discontinuations related to study drug
  - 82% of TransCon PTH patients and 100% of patients in control group reported treatment-emergent adverse events (TEAEs), the majority of which were Grade 1, 2 in severity.
    - One serious related TEAE in the TransCon PTH arm was reported due to a dosing error
    - One death in the TransCon PTH arm was assessed as unrelated to study drug
  - TransCon PTH-treated patients showed a mean decrease in 24-hour urine calcium excretion into the normal range, from 390 mg/24 hours down to 220 mg/24 hours

HPES, Hypoparathyroidism Patient Experience Scales.

Chronic Hypoparathyroidism: Significant Patient Population

Estimated Prevalence: ~200K in these 3 regions

USA

~70k–112k

- 2013, Powers et. al., Prevalence and Incidence of Hypoparathyroidism in the United States Using a Large Claims Database, JBMR
- 2011, Clarke et. al., Co-morbid Medical Conditions Associated with Prevalent Hypoparathyroidism: A Population-Based Study

Europe

~86k–223k

- 2013, Underbjerg et. al., Cardiovascular and Renal Complications to Postsurgical Hypoparathyroidism: A Danish Nationwide Controlled Historic Follow-up Study
- 2015, The Epidemiology of Nonsurgical Hypoparathyroidism in Denmark: A Nationwide Case Finding Study
- 2016, Astor et. al., Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway

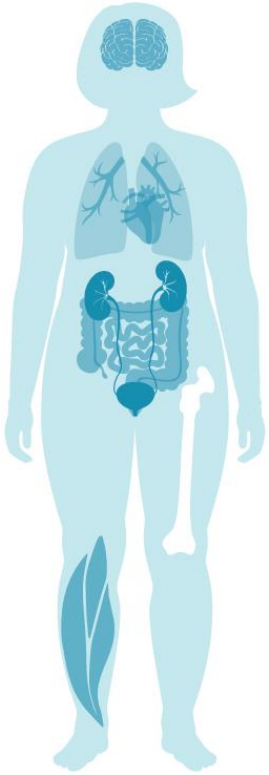
Japan

~25k–32k

- 2017. Shishiba et. al., Prevalence of postsurgical hypoparathyroidism in Japan: Estimated from the data of multiple institutes
- 1999. Nakamura et. al., Prevalence of Idiopathic Hypoparathyroidism and Pseudohypoparathyroidism in Japan
- Ascendis market research

Hypoparathyroidism: Multiple Complications

- Brain fog
- Laryngospasm & bronchospasm
- Infections
- Renal failure
- Numbness & tingling
- Muscle spasms
- Fatigue



- Seizures
- Anxiety & depression
- Heart failure
- Arrhythmias
- Abnormal skeletal dynamics
- Abnormal tissue calcifications
- Pain

Shobak DM et. al. *J Clin Endocrinol Metab.* 2016 June 01;101(6):2300-2312.

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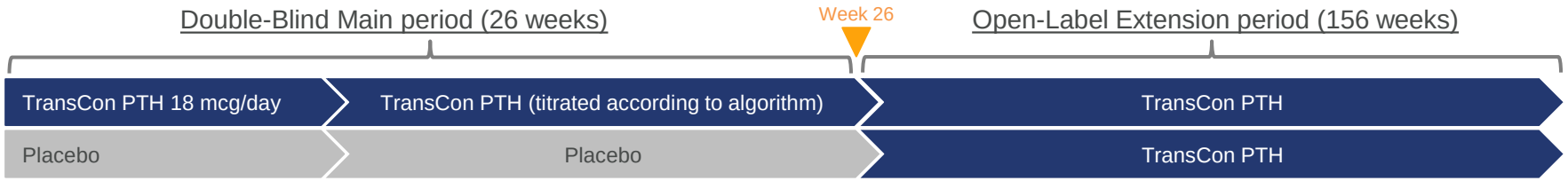
TransCon PTH PaTHway (Phase 3) Trial

Double-blind, placebo-controlled trial with an open-label extension period adults with chronic hypoparathyroidism randomized 3:1 (TransCon PTH:placebo)



Primary Objective

Confirm treatment effect of TransCon PTH in adults with hypoparathyroidism

Key Eligibility Criteria

- Adults with chronic hypoparathyroidism (*i.e.* for at least 26 weeks)
- Age ≥18 years
- Reliant on calcitriol ≥0.50 mcg per day or alfacalcidol ≥1.0 mcg per day, **and** therapeutic elemental calcium ≥800 mg/day for at least 12 weeks prior to screening
- Serum calcium in normal (or just below normal) range: 7.8–10.6 mg/dL (1.96–2.64 mmol/L)
- No PTH or PTHrP therapy within 4 weeks prior to Screening

Countries

- Europe (Germany, Denmark, Norway, Italy, Hungary)
- North America (United States, Canada)

Primary Composite Endpoint at Week 26[1]

Proportion of patients with:

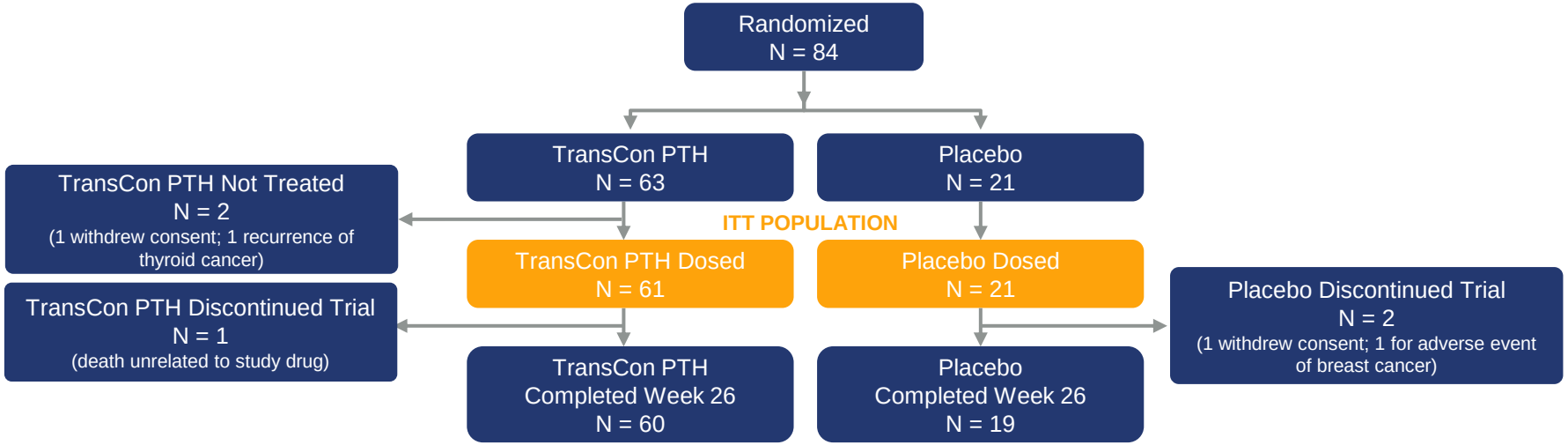
- Serum calcium in the normal range (8.3–10.6 mg/dL) ***and***
- Independence from active vitamin D ***and***
- Independence from calcium supplements[2]

Key Secondary Endpoints at Week 26

- HPES Symptom - Physical domain score
- HPES Symptom - Cognitive domain score
- HPES Impact – Physical Functioning domain score
- HPES Impact – Daily Life domain score
- SF-36 - Physical Functioning subscale score

[1] No increase in prescribed study drug within 4 weeks prior to Week 26 visit.
[2] If needed to meet recommended dietary intake of calcium, it was permitted to take calcium supplements ≤600 mg/day as a nutritional supplement.

PaTHway Trial Patient Disposition



- Intention To Treat (ITT): All randomized patients who received at least 1 dose of randomized treatment
- Safety Analysis Set (SAS): All randomized patients who received at least 1 dose of randomized treatment

Data on file, Ascendis Pharma 2022.

Patients Who Discontinued Trial during Blinded Treatment Period

Randomized Arm	Off Study Day	Off Study Reason
Placebo	30	Withdrew consent
Placebo	62	Breast cancer
TransCon PTH	111	Cardiac arrest

All discontinuations were unrelated to study drug

Data on file, Ascendis Pharma 2022.

Patient Demographics

Demographics and Baseline Characteristics

Characteristics	TransCon PTH (N = 61)	Placebo (N = 21)
Age (years) (n)	61	21
Mean (SD)	49.0 (13.1)	47.3 (11.4)
Age Group (years) – n (%)		
<50	28 (45.9)	14 (66.7)
≥50	33 (54.1)	7 (33.3)
Sex at Birth n (%)		
Female	46 (75.4)	18 (85.7)
Body Mass Index (kg/m^2) (n)	61	21
Mean (SD)	27.3 (5.8)	29.5 (5.7)
Menopausal Status – n (%)	46	18
Postmenopausal	19 (41.3)	3 (16.7)

Data on file, Ascendis Pharma 2022.

Demographics and Baseline Characteristics (continued)

Characteristics	TransCon PTH (N = 61)	Placebo (N = 21)
Race – n (%)		
American Indian or Alaska Native	0	0
Asian	3 (4.9)	2 (9.5)
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	0
White	57 (93.4)	19 (90.5)
Other	1 (1.6)	0
Geographic Region – n (%)		
North America	39 (63.9)	12 (57.1)
Europe	22 (36.1)	9 (42.9)

Data on file, Ascendis Pharma 2022.

Hypoparathyroidism Disease Etiology and Medical History

Characteristics	TransCon PTH (N = 61)	Placebo (N = 21)
Cause of Hypoparathyroidism (HP)		
Acquired from neck surgery	52 (85.2)	18 (85.7)
Autoimmune disease	1 (1.6)	0
Intrinsic genetic defects of the parathyroid glands	3 (4.9)	0
Idiopathic disease	4 (6.6)	3 (14.3)
Other	1 (1.6)	0
Duration of HP (Years) (n)	61	21
Mean	12.0	11.1
Min, Max	1, 56	1, 33
Patient History		
Renal Insufficiency History	5 (8.2)	1 (4.8)
Kidney Stones History	15 (24.6)	4 (19.0)
Ectopic Calcifications History	0	0
Vascular Calcifications History	1 (1.6)	0
Brain Calcification History	1 (1.6)	0
Cataract History	3 (4.9)	0
Seizure History	0	1 (4.8)

Data on file, Ascendis Pharma 2022.

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Baseline Conventional Therapy

Conventional Therapy Total Daily Dose (TDD) at Baseline	TransCon PTH (N = 61)	Placebo (N = 21)
Calcium Supplement/TDD (mg) (n)	61	21
Mean	1748	2105
Min, Max	600, 5000	800, 7200
Calcitriol (Active Vitamin D) /TDD (µg) (n)	53	17
Mean	0.76	0.69
Min, Max	0.5, 2.0	0.5, 1.75
Alfacalcidol (Active Vitamin D) /TDD (µg) (n)	8	4
Mean	2.5	2.0
Min, Max	1.0, 4.0	1.5, 2.5

2 patients did not have eDiary information confirmed by prescription information.
Data on file, Ascendis Pharma 2022.

Baseline Albumin-Adjusted Serum Calcium & 24-Hour Urine Calcium

Lab Summary at Baseline	TransCon PTH (N = 61)	Placebo (N = 21)
Albumin-Adjusted sCa (mg/dL) (n)	61	21
Mean (SD)	8.8 (0.7)	8.6 (0.6)
24-Hour Urine Calcium (mg/dL) (n)	60	21
Mean (SD)	392 (175)	329 (140)

sCA, serum calcium.
Data on file, Ascendis Pharma 2022.

Trial Results

Primary Composite Endpoint at Week 26

PaTHway TRIAL

	TransCon PTH (N = 61)	Placebo (N = 21)
Number of Patients Meeting The Primary Endpoint Criteria at Week 26 (responders)	48	1
Proportion (95% CI), %	78.7% (66.3%, 88.1%)	4.8% (0.1%, 23.8%)
Hypothesis Test: p-value (TransCon PTH vs Placebo) [1]	<0.0001	
Number of Patients Meeting Each Component, (n):		
Albumin-adjusted sCa within the normal range [2]	49	10
Independence from active vitamin D	60	5
Independence from therapeutic doses of calcium supplements	57	1
No increase in prescribed study drug	57	12

Three patients with missing data for at least one of the components are considered as non-responders.

TransCon PTH demonstrated a response rate of 78.7% compared to 4.8% for control (p-value <0.0001)

[1] CMH test controlling for etiology of hypoparathyroidism (post-surgical vs other).
[2] The normal range for albumin-adjusted sCa is 8.3-10.6 mg/dL (2.07-2.64 mmol/L). Patients with missing data on one or more of the criteria are considered as non-responders.
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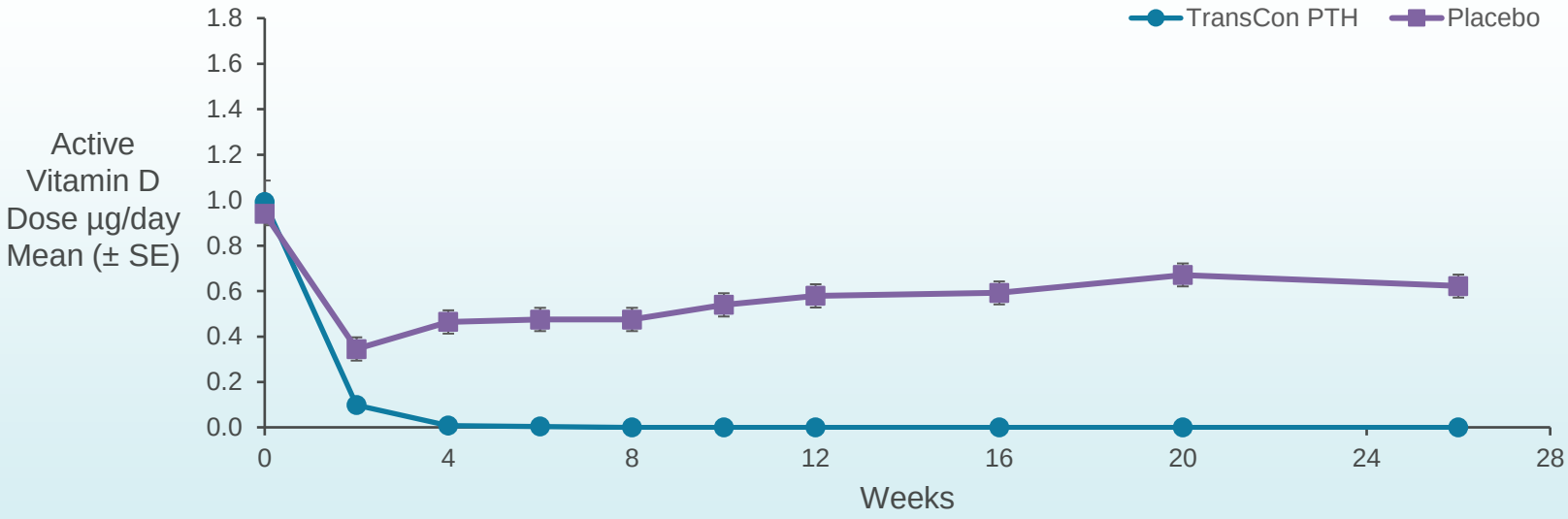
Active Vitamin D Dose (Mean +/- SE) by Visit



TransCon PTH patients discontinued active vitamin D completely within four weeks

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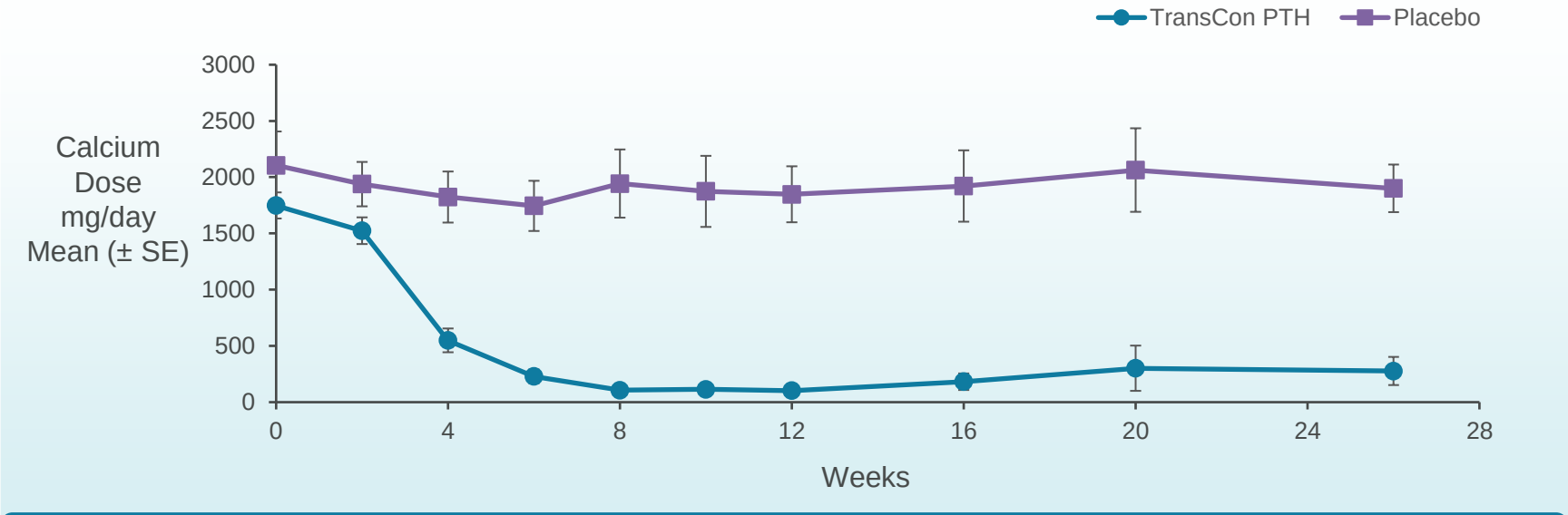
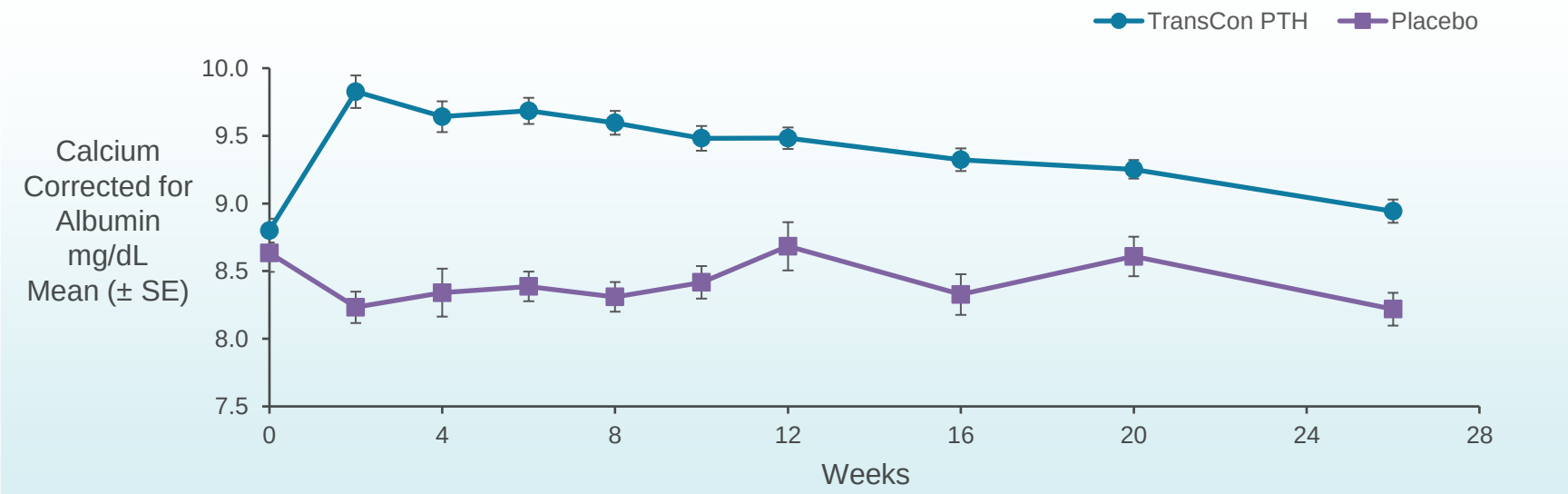
Calcium Supplement Dose (Mean +/- SE) by Visit



TransCon PTH enabled rapid and sustained calcium supplement reduction

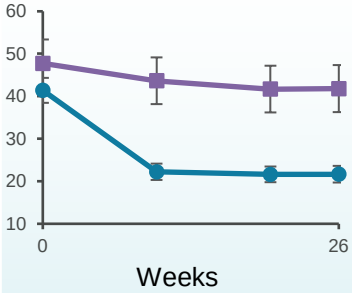
Albumin-adjusted Serum Calcium (Mean +/- SE) by Visit



TransCon PTH patients maintained mean serum calcium levels in the normal range at all study visits

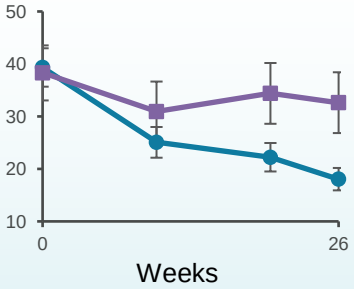
Key Secondary Endpoints: Patient Reported Symptom & Quality of Life Domains

HPES Symptom
Physical domain score



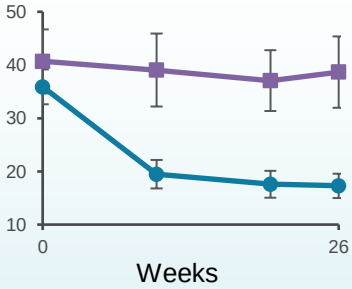
p-value = **0.0038**

HPES Symptom
Cognitive domain score



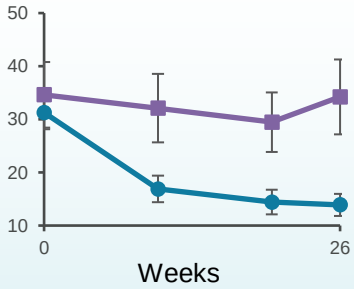
p-value = **0.0055**

HPES Impact
Physical Functioning domain score



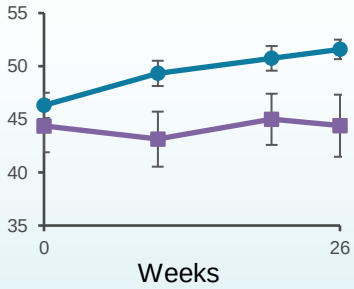
p-value = **0.0046**

HPES Impact
Daily Life domain score



p-value = **0.0061**

SF-36
Physical Functioning subscale score



p-value = **0.0347**

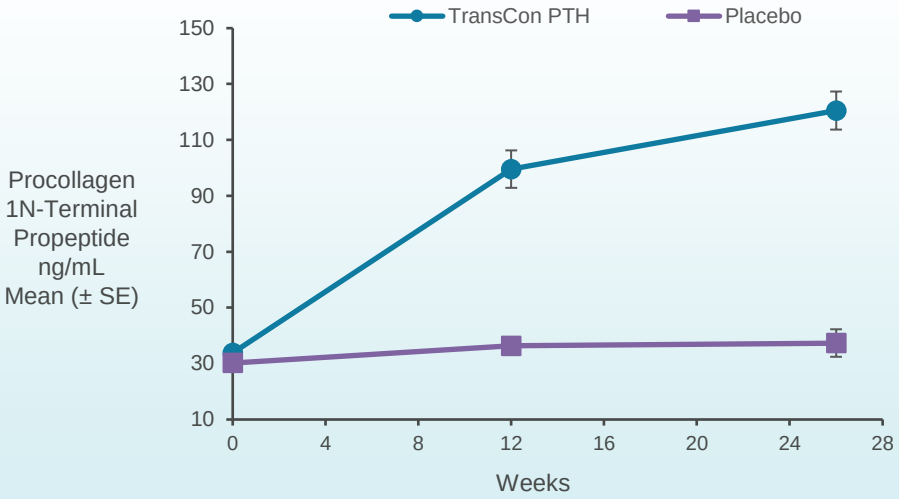
TransCon PTH Placebo

All prespecified key secondary endpoints demonstrated statistically significant improvement compared to control

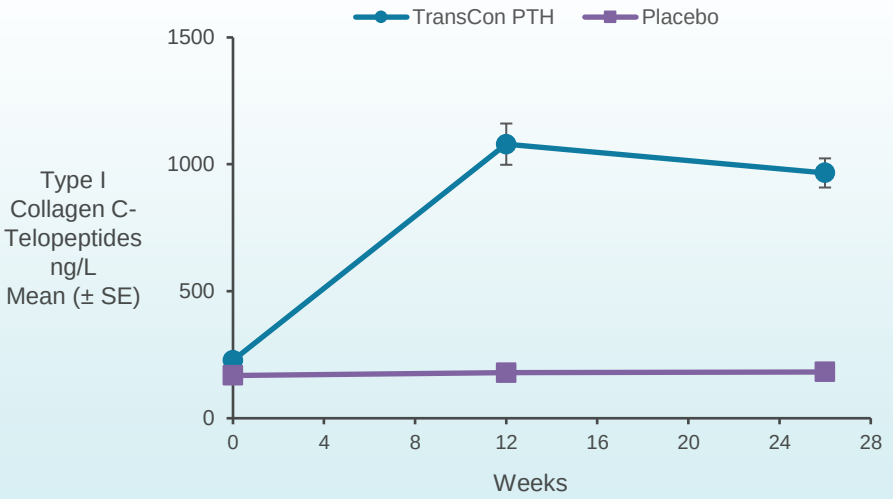
P-values are TransCon PTH vs Control.
For HPES, lower scores indicate improvement; for SF-36, higher scores indicate improvement.
Data on file, Ascendis Pharma 2022.

Bone Turnover Markers: P1NP and CTx (Mean +/- SE) by Visit

Mean P1NP



Mean CTx



Similar pattern exhibited at Week 26 in Phase 2 PaTH Forward Trial

P1NP, procollagen type 1 N-terminal propeptide
CTx, C-terminal telopeptides of type I collagen

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Safety Results

Overall TEAE Summary

TEAE Summary	TransCon PTH (N = 61); n (%)	Placebo (N = 21); n (%)
Treatment-Emergent Adverse Events (TEAE)	50 (82.0)	21 (100.0)
Serious TEAE	5 (8.2)	3 (14.3)
Severity*		
Grade ≥3	2 (3.3)	1 (4.8)
Grade 2	21 (34.4)	9 (42.9)
Grade 1	27 (44.3)	11 (52.4)
Related TEAE	30 (49.2)	8 (38.1)
Serious Related TEAE	1 (1.6)	0
TEAE Related to Hyper- or Hypocalcaemia Leading to ER/Urgent Care Visit and/or Hospitalization	4 (6.6)	2 (9.5)
TEAE Leading to Discontinuation of Study Drug	1 (1.6)**	2 (9.5)

*In the severity categories, patients are displayed for the highest severity category only.
**Death due to cardiac arrest
Data on file, Ascendis Pharma 2022.

Treatment-Emergent Adverse Events (≥5 patients in total)

Preferred Term	TransCon PTH (N = 61)	Placebo (N = 21)
Patients with at least one TEAE, n (%)	50 (82.0)	21 (100.0)
TEAEs		
Injection site reaction	19 (31.1)	0
Headache	13 (21.3)	2 (9.5)
Hypocalcaemia	6 (9.8)	9 (42.9)
Fatigue	9 (14.8)	5 (23.8)
Paraesthesia	11 (18.0)	3 (14.3)
Muscle spasms	7 (11.5)	3 (14.3)
Nausea	7 (11.5)	2 (9.5)
Arthralgia	6 (9.8)	2 (9.5)
Diarrhoea	6 (9.8)	1 (4.8)
Hypercalcaemia	6 (9.8)	0
Constipation	4 (6.6)	1 (4.8)
Insomnia	4 (6.6)	1 (4.8)

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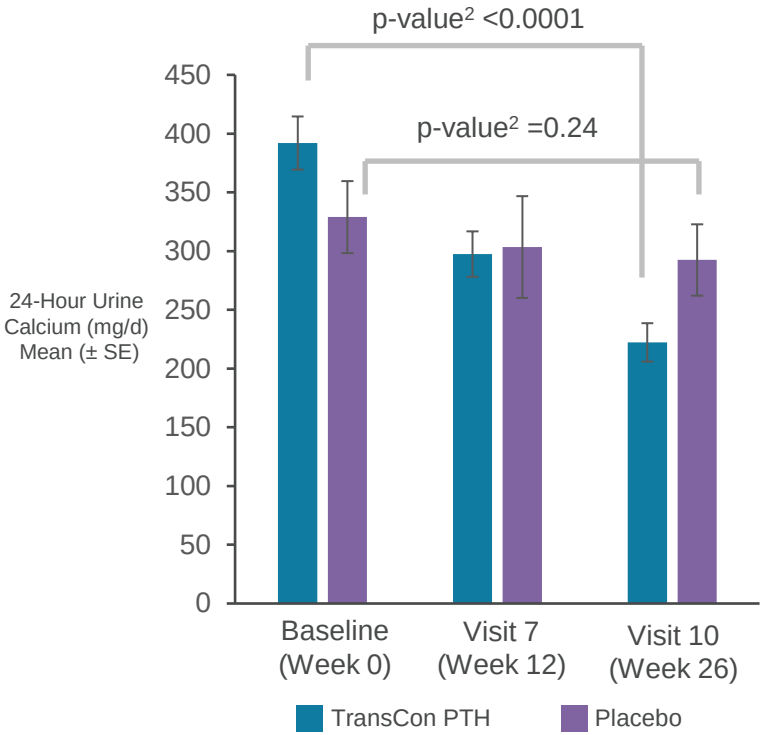
24-Hour Urine Calcium (mg/d) by Visit



24-Hour Urine Calcium (mg/d), Change from baseline at Week 26	TransCon PTH (N = 61)	Placebo (N = 21)
ANCOVA Model (n) [1]		
LS Mean (SE), mg/d	**-154** (21)	**-64** (32)
95% CI for LS Mean	(-197, -112)	(-131, 2)
Difference in LS Means (SE)	**-90** (32)	
95% CI for Difference in LS Means	(-155, -25)	
p-value (TransCon PTH vs Placebo)	0.0085	

[1] The ANCOVA model with unequal variance includes the change from baseline as the response variable, treatment and etiology of HP as fixed effects and baseline value of the parameter as a covariate.
[2] p-values from t-test.
Data on file, Ascendis Pharma 2022.

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Program Status and Next Steps

- Two Open-Label Extension trials continuing
  - 57 of 59 patients remain in PaTH Forward Trial after two years
  - All 79 patients who completed the blinded period continue in the PaTHway Trial
- Engage with regulatory authorities regarding registration plans for US and EU
  - Anticipated NDA submission to FDA during Q3, 2022
  - Anticipated MAA submission to EMA during Q4, 2022
- Continue adult TransCon PTH trial in China*
- Japan Phase 3 top-line data expected in Q3, 2022
- Plan to initiate pediatric TransCon PTH trial in Q4, 2022

*In development in Greater China through strategic investment in VISEN Pharmaceuticals.

Thank you

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